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Original Research Article

Thyroid Profile of Childhood Tuberculosis Treated with Anti Tuberculosis Drug During Intensive Phase

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Abstract

Background: Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. The incidence is 10 % in children. Tuberculosis has high morbidity and mortality, which needs adequate treatment. However, one of the side effects of anti-tuberculosis drugs is thyroid hormone dysfunction which can interfere children's quality of life. However, research about the effect of drugs on thyroid hormone profile in children with TB are very limited and this is the first study on the effect of thyroid function in children treated with tuberculosis drugs.

Objective: To determine the effect of anti-tuberculosis drug treatment on thyroid hormone profile in paediatric tuberculosis.

Methods: A one-group pretest-posttest design study of 50 patients was conducted at the Semarang Health Center for the period January 2021-June 2021. Patient with MDR TB or other history of thyroid disease or history of thyroid drug consumption were excluded. Thyroid function tests of TSH, FT4 and T3, in TB children were measured before treatment and two months after administration. The data were analysed descriptively and a comparative test was performed using SPSS 25.

Results: There were significant differences in FT4 and T3 serum levels before and two months after tuberculosis drug administration, but not in TSH levels. Thyroid hormone levels before and two months after treatment showed euthyroid status in 44 vs 42 patients, respectively.

Conclusion: Two months of intensive phase of tuberculosis treatment in children decreased the serum FT4 and T3 levels but still in the normal range of FT4 and T3. There were no changes in the serum TSH level before and after the treatment.

Keywords: *Thyroid Profile, Tuberculosis Drugs, Tuberculosis, FT4, TSH*
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INTRODUCTION

Tuberculosis in the child is still a growing problem in developing countries such as Indonesia. World Health Organization (WHO) reported that in 2011, eleven percent of all tuberculosis cases were in children.[1] Although multiple efforts have been done by the government to prevent the tuberculosis, Indonesia is still ranked third in the world with the prevalence of twelve percent tuberculosis in children. With its economic burden, tuberculosis in children is an important health problem for the future of the country.[1,2]

Tuberculosis is a systemic infectious disease that can affect all organs, including the thyroid gland, directly through bacterial infection to the organs [3] or indirectly caused by the medication.[4] Direct infection of MTB causes local pathological abnormality in the thyroid gland[8,9] while several tuberculosis medications may cause thyroid gland dysfunction, such as ethionamide, paraaminosalicylate sodium (PAS) and rifampicin.

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Table 1. Characteristics of the subjects

Variable		**Subject** (n=50)
Age in years (median, min-max)		9.2(5.5 – 14)
Sex		
	Male	28 (56%)
	Female	22(44%)
Nutritional status*		
	Malnutrition	11 (22%)
	Normal	39 (78%)
Contact status		
	Yes	28 (56%)
	No	22 (44%)
Tuberculin test result		
	Positive	46 (92%)
	Negative	4 (8%)
Main Clinical Manifestation		
	Weight loss or faltering	36 (72%)
	Cough	9 (18%)
	Malaise	4 (8%)
	Fever	0 (0%)
Chest x-ray		
	Infiltration	5 (10%)
	Enlargement of hilum node	22 (44%)23(46%)
	Infiltration and Enlargement of hilum node	

*Nutritional status was determined based on the BMI according to the standard guidelines.

Table 2. Before and after tuberculosis drugs therapy intensive phase

Variable		**Before treatment**	**After treatment**	***p***
Weight, in kg (mean±SD)		25,5±8,9	26,7±9,1	0.000[#]
Height, in cm (median min-max)		126 (106-161)	127 (108-161)	0.000*
BMI, in kg/m^2 (median min-max)		14.8 (12.05-21,91)	15.29 (12.23-22.10)	0.000*
Nutritional status				0.000[$]
	Malnutrition	11 (22%)	8 (16%)	
	Normal	39 (78%)	42 (84%)	
TSH serum level, in µIU/ml,		5.3 (0.5-24.4)	4.95 (1.4-13.6)	0.687*
Free T4 serum level, in ng/dl,		1.6 (1.0-2.1)	1.4 (0.8-2.2)	0.000*
T3 serum level, in ng/ml,		0.69 (0.49-1.66)	0.62 (0.37-1.66)	0.000*

TSH *thyroid stimulating hormone*
(#) paired t-test, (*) Wilcoxon [$] chi-square

Table 3. Effect of nutritional status on serum levels of TSH, FT4 and T3 before and after 2 months treatment

	TSH level (µIU/ml)		fT4 level (ng/dL)		T3 level (ng/mL)	
Before treatment						
		p=0.355[a]		p=0.472[a]		p=0.925[a]
Malnutrition	5.4 (2.0-17.4)		1.9 (1.1-2.0)		0.6 (0.4-1.3)	
Normal	5.0 (0.5-24.4)		1.7 (1.0-2.1)		0.7 (0.5-1.6)	
After treatment						
		p=0.412[a]		p=0.576[b]		p=0.427[a]
Malnutrition	6.0 (1.4-12.2)		1.3 □ 0.29		0.6 (0.5-1.6)	
Normal	5.0 (1.6-13.6)		1.4 □ 0.33		0.6 (0.3-1.6)	

([a]) *Mann Whitney*, ([b]) *independent t test*

There are not many studies to measure the effect of tuberculosis infection or medication on thyroid gland, especially in children. Rifampicin, a core drug of tuberculosis treatment, induced hypothyroidism through increased metabolic clearance rate of thyroid hormone due to enhanced hepatic metabolism and increased biliary excretion of iodothyronine conjugates.[20] However, its mechanism remains unclear in children.

Thyroid function is necessary for the child as a neuromuscular system modulator, growth, puberty and bone growth. It is also necessary for energy metabolism in several important organs through thyroxine (T4) and *triiodothyronine* (T3) hormone under the control of *Thyroid-stimulating hormone* (TSH).[5] As indirectly, the measurement of these hormones may express the thyroid function. Studies showed that in adults patients with bacteriology confirmed tuberculosis, thyroid dysfunction

was found in the early diagnosis and the thyroid function improved after the therapy while patients with hypothyroid had higher risks to get infected with tuberculosis.[7]

Growth and development are characteristics of children controlled by thyroid hormone in their regulation which mainly affected during infection of tuberculosis while there were not a lot of study to examine the effect of tuberculosis drugs on thyroid profile in patients. The aim of this study was to measure the thyroid profile in children with tuberculosis treated with 2 month-intensive tuberculosis drugs regiment.

MATERIAL AND METHODS

This study was conducted in Lung Health Center Semarang Indonesia as the reference center for tuberculosis patients. A total of 50 patients older than 5 years old fulfilling the inclusion criteria were included in this study. The inclusion criteria were children diagnosed with tuberculosis and received tuberculosis treatment; the children were generally without any known micronutrient diseases. All the patients lived in the urban area in Semarang without any history of lack of iodine. The patients were excluded if they were infected with multi drug resistant (MDR) TB, diagnosed with thyroid disorder before the tuberculosis treatment, the patients consumed any medication that may affect the thyroid hormone or the patients suffered any chronic diseases such as nephrotic syndrome, malignancies, autoimmune disease or congenital heart diseases or infected with extra pulmonary tuberculosis. The diagnosis of tuberculosis was based on positive tuberculin test, clinical sign of tuberculosis infection, chest x-ray suggestive of tuberculosis, or positive bacteriology examination of sputum or positive molecular testing. The participants were included in the study after the parents or guardian had agreed to participate in the study after signing the informed consent.

Demographical data and anthropometric status were obtained before the treatment using standard measurement with SECA® digital weighing scale (Seca, Deutschland) and stadiometer. Nutritional status was determined based on BMI as normal or malnutrition. The chest x-ray was performed according to standard operating procedure and the interpretation was performed by the clinician and radiologist using guidelines from the Union. The serum levels of TSH, FT4 and T3 were measured using ELISA from patients before and two months after the treatment with standard intensive phase regiments of tuberculosis according to Indonesian national tuberculosis guidelines which include rifampicin, INH and pyrazinamide.

Before the study, ethical clearance was obtained from Health Research Ethical Committee from Diponegoro University/Kariadi General Hospital with register number 295/EC/KEPK/FK-Undip/VIII/2021. All parents or guardian who did not agree to participate after informed consent would still receive all the treatment for tuberculosis.

Demographic data was analyzed and shown in table and analysis to compare the differences of thyroid profile before and after 2 months intensive phase tuberculosis treatment was performed with Wilcoxon test, paired t-test and chi-square test according to its data type using SPSS 25.

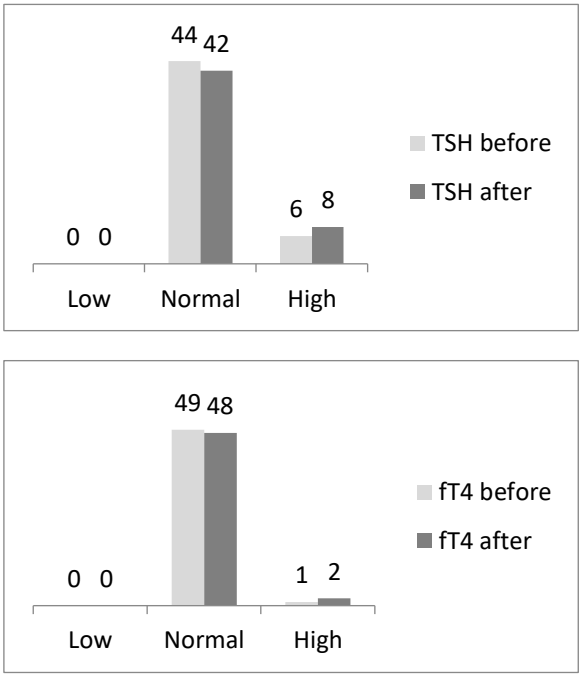

Figure 1. Difference of serum levels of TSH and FT4 before and after tuberculosis drug treatment. A. TSH serum level before and after therapy. B. FT4 serum level before and after therapy.

RESULTS

This study included 50 children aged from 5.5 to 14 years old with almost equal number of male and female. The majority of the patients were in normal nutritional status and almost all of them were positive for the tuberculin test. Interestingly more than two third of the patients had clinical characteristics of growth faltering or weight loss. Majority of the patients had enlargement of lymph nodes from the chest x-ray typical of tuberculosis. More details can be seen in table 1.

In general, the weight of the children was significantly increased followed by a significant difference in the number of children that had better nutritional status. In addition, there was a significant difference of FT4 and T3 serum level before and after two months of treatment, but not for TSH levels (table 2).

Nutritional status is important condition related to the thyroid profile. We compared the differences of TSH, FT4 and T3 serum level based on the nutritional status before and after the tuberculosis treatment. There was no significant different before and after the tuberculosis treatment in either malnutrition and normal nutritional status as detailed in table 3.

In general, majority of the children had normal TSH and FT4 serum levels before the start of the tuberculosis treatment. There was one child with increased FT4 before and two children after treatment.

DISCUSSION

In our study, ten percent of the children had subclinical hypothyroid with higher TSH serum levels without reduced levels of FT4 and one child with slightly increased FT4 with normal TSH level. After two months

of treatment, fourteen percent of patients had higher TSH serum levels while four percent of patients showed lower FT4. Our result is in concordance with the previous study, which showed that serum T3 and FT4 levels decreased in patients who received intensive phase of tuberculosis drugs, although the patients had no clinical signs of symptoms of thyroid abnormalities. A study in adult patients showed that there was a bidirectional correlation between thyroid and tuberculosis as patients with hypothyroidism had 3.6 times higher chance to develop TB than those without any thyroid abnormalities, while patients with TB had 2.5 times higher chances to develop hypothyroid.[7]

The previous study showed that malnutrition affected the thyroid function in children as malnutrition children have lower thyroid serum levels.[12] Malnutrition is one of the main manifestations of TB, which may explain the abnormalities of thyroid function in TB. In malnutrition, as an adaptive response, the thyroid structure changes, which causes disturbance in thyroid gland function, resulting in reduced thyroid hormone in circulation.[14,15] However, in our study, there was no difference of nutritional status in our patients. It is possibly that because all our patients were in mild malnutrition and treated early. A previous study showed that the level of severity in hypothyroid was affected by the severity of malnutrition, as subjects with severe malnutrition have lower thyroid hormone serum levels compared to subjects with mild or moderate malnutrition.[16]

Treatment of TB with rifampicin may affect thyroid function. A previous study in adults revealed that thyroid function reduced after two weeks of treatment with rifampicin, which later resolved two to four weeks after the treatment stopped.[11] Other studies even showed that the recovery after the treatment with rifampicin might take longer to two months after stopping the treatment. However, another study in thirteen healthy volunteers who received rifampicin for 28 days showed that there was no significant changes of serum TSH or FT4 level although there were increased volume of thyroid gland and antipyrine clearance. This hypothesize that rifampicin increased the thyroid hormone clearance in liver but it is compensated by normal thyroid gland with normal serum TSH and FT4 levels.

Our study showed that there were significant difference of serum FT4 and T3 level before and after two months treatment with antituberculotic drugs without difference in serum TSH level. We hypothesize that the difference was caused by the trapping of iodide in thyroid gland as side effect of the tuberculosis drugs. The iodide trapping inside the thyroid gland reduce the number of iodide available for thyroid hormone synthesis including the T3 and FT4 synthesis. Further study showed that the tuberculosis drugs with rifampicin as one of the regiments induced the binding of T4 and T3 by proteins such as *thyroxin binding globulin*, *transthyretin,* and albumin causing the reduction of serum T4 and T3 level. [19,20]

The limitations in our study were the follow-up limited time which was only two months of treatment and there was no examination of thyroid autoantibody such as thyroglobulin antibody (Tg Ab) or thyroid peroxidase antibody (TPO Ab) to exclude other causes of thyroid abnormality such as Hashimoto thyroiditis. Other factors that influences thyroid function in children were not examined in our subjects, such as micronutrient intake, the status of micronutrient deficiencies, and nutritional status of the subject's family. Further study with an examination of thyroid autoantibody, longer follow-up and other factors such as detailed nutritional status may be necessary to examine the relation of thyroid and tuberculosis specifically with the treatment side-effects.

CONCLUSION

Two months of the intensive phase of tuberculosis treatment in children decreased the serum FT4 and T3 levels, but were still in the normal range. There was no significant difference in the serum TSH level before and after the treatment.

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